EXHIBIT 4

HIGH LIGHT
CME

Increased rate of major malformations in offspring exposed to valproate during pregnancy

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Abstract—*Objective:* To determine the rate of occurrence of major malformations in infants whose mothers had taken the drug valproic acid (VPA) as monotherapy during the first trimester of pregnancy and had enrolled in the North American Antiepileptic Drug Pregnancy Registry. *Methods:* Data were collected from pregnant women throughout the United States and Canada through telephone-based interviews. Each woman was interviewed at enrollment, at 7 months' gestation, and postpartum. With her written permission, the medical records of each mother and her infant were obtained. The major malformations tabulated were those identified at or before 5 days of age. The prevalence of congenital malformations among offspring of monotherapy VPA-exposed women was compared with that among infants of women exposed to all other antiepileptic drugs (internal comparison group) and with that among newborns in the Active Malformations Surveillance Program at Brigham and Women's Hospital (external comparison group). *Results:* Sixteen affected cases were identified among 149 VPA-exposed women (proportion: 10.7%; 95% CI: 6.3 to 16.9%). The prevalence in the internal comparison group was 2.9% (95% CI: 2.0 to 4.1%; odds ratio: 4.0, 95% CI: 2.1 to 7.4; $p < 0.001$). Assuming a 1.62% prevalence in the external comparison group, the relative risk of having an affected offspring for VPA-exposed women was 7.3 (95% CI: 4.4 to 12.2; $p < 0.001$). *Conclusion:* Maternal exposure to valproic acid during the first trimester of pregnancy significantly increased the risk of major malformations.

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Exposure to anticonvulsant drugs during pregnancy is potentially harmful to a fetus.[1] However, there are only a few well-designed prospective studies. Pregnancy registries are a new, efficient approach to obtaining information about the fetal effects of exposures to specific drugs as monotherapy.

Valproic acid (VPA) became available clinically in the United States in 1978 as an immediate-release formulation (Depakene Convulex capsule; Abbott Laboratories, Abbott Park, IL) for the treatment of absence seizures.[2,3] In 1983, another formulation, divalproex sodium (Depakote; Abbott Laboratories), was introduced. It is an enteric-coated, stable coordination complex of VPA and valproate sodium. VPA is an 8-carbon two-chain fatty acid that is absorbed rapidly after oral administration and has a short half-life.[5] Although VPA's mechanism of action is not established, it may increase brain concentrations of γ-aminobutyric acid.[4] VPA use has expanded to include treatment of complex partial and other seizures, prevention of migraine headache, and treatment of acute mania associated with bipolar disorder.[6]

A report suggesting teratogenicity of VPA in humans was published in 1980.[7] In 1982, a significant (20-fold) risk for the occurrence of spina bifida after exposure to VPA during pregnancy was identified by a regional birth defects surveillance program.[8] In 1984, the term "fetal valproate syndrome" was suggested to refer to a constellation of minor and major malformations[9]: a pattern of facial manifestations (epicanthal folds, flat nasal bridge, small upturned nose, long philtrum, and thin upper lip), multiple major malformations, and CNS dysfunction.[10] Similar malformations occur in children exposed to other anticonvulsants such as phenobarbital, phenytoin, and carbamazepine, but no systematic study has determined whether malformations in VPA-exposed children are distinctive. A common major malformation attributed to exposure to VPA was neural tube defects (NTDs).[8,11-17] The risk of an NTD may be as

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high as 5% at high VPA exposures.[18] Other congenital malformations associated with this exposure have included heart defects, oral clefts, genital abnormalities, and limb defects.[10,19-25]

We have performed a prospective study of the rate of occurrence of major malformations identified at birth in infants whose mothers had taken valproate as monotherapy and had enrolled in the North American Antiepileptic Drug (AED) Pregnancy Registry.

Methods. The North American AED Pregnancy Registry is an ongoing surveillance system of pregnant women exposed to anticonvulsant drugs.[26] Women were interviewed at enrollment, at 7 months' gestation, and postpartum. Medical records were obtained about the mother's medical history and any malformations identified in the infant. The protocol and criteria for the release of findings were established prospectively by an external Scientific Advisory Committee.[26] The informed consent document, read and signed by each woman who enrolls in the Registry, was reviewed and approved each year by the Human Studies Committee of the Massachusetts General Hospital.

Exposed participants. We studied only infants exposed to VPA monotherapy during the first trimester of pregnancy. We included elective abortions for structural abnormalities and stillbirths. To minimize recall bias, we included only women who did not know, at time of enrollment, whether the fetus had a malformation or not. We excluded women who enrolled with some knowledge of the status of the fetus, typically after having prenatal screening by ultrasound. Women who enrolled after having had prenatal screening by either chorionic villus screening or nuchal translucency were also excluded. A major malformation was defined as a structural abnormality with surgical, medical, or cosmetic importance.[27] Physical features not considered a major malformation were 1) minor anomalies; 2) deformations; 3) physiologic features due to complications of prematurity, such as undescended testes; 4) birth marks; 5) genetic disorders and chromosomal abnormalities; 6) any finding by prenatal sonography, such as absence of one kidney, that was not identified by an examining pediatrician; 7) an incidental finding within 5 days of delivery, at surgery or autopsy, such as a unilobe right lung, that had not been detected in clinical evaluations. The written descriptions of the findings from the examinations of each infant were reviewed separately by two registry dysmorphologists who were blinded to exposure status. Any disagreement was resolved by consensus.

Comparison groups. There were two comparison groups. The first, the internal comparison group, comprised infants of enrolled mothers who had taken any monotherapy AED, other than VPA, during the first trimester of gestation. The mothers in the internal comparison group, like the mothers taking VPA, were not aware of the health status of the fetus (i.e., presence or absence of a congenital anomaly) at the time of the baseline interview. The second comparison group, the external comparison group, comprised newborns with major anomalies identified in the Active Malformations Surveillance Program at Brigham and Women's Hospital in Boston, MA, which used the same inclusion/exclusion criteria as the registry.[28] For this comparison, the infants whose malformations were associated with chromosome abnormalities or a hereditary disorder were excluded.

Statistical methods. Statistical analyses were carried out with the software Stata (version 8.2).[29] For continuous data, means and standard deviations were calculated, and potential differences were tested with simple linear regression. In the case of ordinal variables, multiple logistic regression was used to obtain odds ratios (ORs) and their 95% CIs and to derive adjusted p values.

Results. Three thousand four hundred forty-one women enrolled in the AED Pregnancy Registry from February 1, 1997, through November 20, 2003. Fifty-seven percent of these women (n = 1,956) reported having taken an anticonvulsant drug as monotherapy during the first trimester and reported having either a liveborn or stillborn infant or a pregnancy that was terminated electively because of a fetal abnormality. VPA monotherapy was used by 235 women (12.0% of monotherapy-exposed group of 1,956). One hundred forty-nine (63%) of these women were unaware of the health status of the fetus at the time of the baseline interview (i.e., "pure" prospective). These women constitute the "VPA-exposed" group.

Sixteen infants with confirmed major malformations (table 1) were identified in the VPA-exposed group (proportion: 10.7%; 95% CI: 6.3 to 16.9%). Two of the children (Cases 2,321 and 2,978) were African American, and 14 were Caucasian. All mothers had taken VPA because of seizures (mean age at first seizure 15 years, range 10 to 21 years). The average dosage of VPA used by mothers of malformed and nonmalformed infants was not different statistically (mothers of malformed infants: 1,033.3 mg, SD: 434 mg; mothers of nonmalformed infants: 983.2 mg, SD: 431 mg; $p = 0.69$). After excluding mothers of infants with the less severe malformations (Cases 2,118, 2,321, 2,364, 2,978, 3,225, and 3,560; see table 1), this comparison remained insignificant ($p = 0.28$). The mothers of all 16 infants took either prenatal vitamins/multivitamins or supplemental folic acid in the periconceptional period. The mother who had a baby with penoscrotal hypospadias was the only smoker in this group. She consumed 1 pack of cigarettes per day during the periconceptional period.

Twins 1,181a (male) and 1,181b (female) were dizygotic but concordant for their phenotype (lumbosacral spina bifida). Case 3,445 had a severe form of congenital heart defect (pulmonary atresia, ventricular septal defect [VSD], and tricuspid valve stenosis), which resulted in death 12 days after birth. Newborn 2,712 had multiple congenital anomalies, including VSD.

Internal comparison. The prevalence at birth of major malformations among the infants of the 149 VPA-exposed women was compared with that of 1,048 women exposed to all other AED monotherapies (internal comparison). The two groups were very similar in terms of their demographic characteristics and prenatal exposures (table 2). The prevalence of major malformations among the internal comparison group was 2.9% (95% CI: 2.0 to 4.1%). Therefore, there was a fourfold increased risk for having an offspring with a major birth defect for VPA-exposed women compared with those taking other AEDs (OR: 4.0; 95% CI: 2.1 to 7.4; $p < 0.001$).

External comparison. The number of newborns with major anomalies observed among VPA-exposed women was compared with the number of cases expected on the basis of prevalence in the Active Malformations Surveillance Program at Brigham and Women's Hospital[28] and other hypothetical alternative rates (i.e., from 2 to 7%). With use of the 1.62% population prevalence rate of nongenetic major malformations at Brigham and Women's Hospital, the relative risk of having an affected offspring among VPA-exposed women was 7.3, with 95% CI ranging from 4.4 to 12.2 (one sided $p < 0.001$). The risk continued to be significant if the population prevalence rate of major birth defects was <6.5%.

Discussion. The findings of this study show that the use of VPA during the first trimester of pregnancy significantly increased the risk of major con-

Table 1 Characteristics of cases with major congenital malformations exposed to valproic acid during early gestation

Study no.	Dosage at conception, mg	Birth status	Major malformation
1,085	1,000	Live	Tetralogy of Fallot, pulmonary atresia
1,181a	Epival 1000	Pregnancy terminated at 18 wk	Lumbosacral spina bifida, affected twins (diagnosed by ultrasound)
1,181b	Epival 1000	Pregnancy terminated at 18 wk	Lumbosacral spina bifida, affected twins (diagnosed by ultrasound)
2,118	1,000	Live	Atrial septal defect, bicuspid aortic valve
2,321	500	Live	Postaxial polydactyly, type B
2,364	750	Live	Bilateral inguinal hernia
2,414	2,000	Live	Lumbosacral spina bifida
2,547	1,500	Live	Hypospadias (penoscrotal location), microcephaly, and developmental delay*
2,712	1,250	Live	Multiple congenital malformations (including developmental delay, failure to thrive, hypotonia, mitral valve abnormality, triphalangeal thumbs)
2,978	750	Live	Equinovarus club foot deformity
2,997	750	Pregnancy terminated	Bilateral multicystic dysplastic kidneys (diagnosed by ultrasound)
3,225	1,375	Live	Penoscrotal hypospadias
3,445	250	Neonatal death at 12 d of age	Pulmonary atresia, VSD, tricuspid valve stenosis
3,456	750	Live	Bilateral inguinal hernia
3,560	750	Live	Lambdoid suture synostosis
3,858	Depakote sprinkles 125, 13×/d	Live	Metopic synostosis, multiple heart defects: VSD, pulmonary valve stenosis, atrial septal defect

* Developmental delay assessed during follow-up.

Epival = brand name for divalproex sodium in Canada; VSD = ventricular septal defect.

genital malformations. Our findings are also in agreement with several previous reports that showed that VPA was associated with adverse outcomes more frequently than other AEDs.[17,30-35] Although most of these studies were carried out retrospectively, the findings have been remarkably consistent. One notable and new finding in our study was the occurrence in two infants of pulmonary atresia, a severe heart defect. The suggested increased frequency of craniosynostosis, especially metopic synostosis,[36] was validated.

There are several limitations of this study. First, for the external comparison control subjects from the Active Malformations Surveillance Program, the details available from the review of each infant's medical records were, on average, more extensive than the information obtained by the AED Pregnancy Registry by mail from the physician of the infant of the enrolled mother. To address this limitation, the AED Pregnancy Registry employs currently the same method of collecting information for both newly enrolled control subjects and anticonvulsant-exposed infants. A second limitation is the fact that the external control subjects from the Active Malformations Surveillance Program at Brigham and Women's Hospital and the internal control subjects from the AED Pregnancy Registry did not include very many women with epilepsy (or a mood disorder) who were not being treated with anticonvulsant drugs during pregnancy, a theoretical confounder. Whereas at least one study[37] has suggested that women with epilepsy have an increased risk for having malformed infants, unrelated to the medication taken, several others[1,38,39] do not support that hypothesis.

Third, another limitation of this, and other pregnancy exposure, registries is that initially the only outcome that can be assessed is the frequency of all malformations, not specific malformations, such as spina bifida, a well-known consequence of maternal exposure to VPA. To establish correlations, such as a threefold increase in the occurrence of a malformation with a frequency of 1 in 1,000 (like spina bifida or cleft lip), at least 8,329 monotherapy VPA-exposed infants of "pure" prospective mothers must be enrolled to establish this correlation with 80% power.[26] Fourth, the North American AED Pregnancy Registry relies on women who enroll voluntarily by calling the toll-free number to provide their exposure and outcome information. Other AED pregnancy registries (i.e., UK Epilepsy and Pregnancy Register,

Table 2 *Comparison of maternal and newborn characteristics of women exposed to valproic acid and to all other antiepileptic monotherapy drugs during early pregnancy*

Characteristic	Valproate, n = 149	All other AEDs, n = 1,048	Unadjusted odds ratio (95% CI)
Child male	80 (53.7)	536 (51.2)	1.1 (0.8–1.6)
Married	77 (76.2)	663 (89.4)	0.9 (0.8–0.9)
Mother's education			
≤grade 12	18 (24.0)	96 (18.3)	2.4 (0.9–5.8)
Some college, junior college graduate	19 (25.3)	140 (26.7)	1.7 (0.7–4.1)
College graduate, 4-y	30 (40.0)	186 (35.5)	2.1 (0.9–4.7)
Post college	8 (10.7)	102 (19.5)	Ref.
Maternal age, mean (SD); y	29 (6)	30 (5)	1.0 (0.9–1.0)
Gravida, mean (SD)	2 (1)	2 (1)	0.9 (0.8–1.0)
Child Caucasian	123 (83.1)	912 (88.7)	0.6 (0.4–1.0)
Father Caucasian	118 (80.3)	879 (85.6)	0.7 (0.4–1.1)
Age at first seizure, mean (SD); y	13.0 (6)	16.9 (8)	0.9 (0.9–0.9)
Seizures during pregnancy	33 (24.4)	358 (36.9)	0.6 (0.4–0.8)
Prenatal vitamins or multivitamins	115 (78.2)	861 (84.2)	0.7 (0.4–1.0)
Folic acid supplement	106 (71.6)	649 (63.8)	1.4 (0.9–2.0)
Cigarette smoking			
None	119 (79.9)	885 (86.4)	Ref.
>none to <½ pack	10 (6.7)	55 (5.4)	1.4 (0.6–2.6)
≥½ pack to <1 pack	10 (6.7)	31 (3.0)	2.4 (1.1–4.9)
≥1 pack	9 (6.0)	42 (4.1)	1.6 (0.7–3.2)
Yes, but unknown	1 (0.7)	11 (1.1)	0.7 (0.1–3.5)
Alcohol			
None	124 (83.2)	801 (78.5)	Ref.
Moderate: >none to <5 drinks/wk	18 (12.1)	198 (19.4)	0.6 (0.3–1.0)
≥5 drinks/wk	4 (2.7)	13 (1.3)	2.0 (0.6–5.7)
Unknown	3 (2.0)	9 (0.9)	2.2 (0.5–7.3)
Child with confirmed major congenital anomaly*	16 (10.7)	31 (2.9)	4.0 (2.1–7.4)
Child birth wt,† mean (SD); g	3,246 (681)	3,366 (608)	1.0 (0.9–1.0)
Child length,† mean (SD); cm	51 (4)	51 (4)	1.0 (1.0–1.1)
Child head circumference,† mean (SD); cm	34 (2)	35 (3)	0.9 (0.8–1.0)

Numbers in parentheses are percentages, except when otherwise noted. SDs were rounded to the nearest decimal. Unadjusted odds ratios did not differ from the adjusted ones that were obtained using multiple linear (continuous variables) or multiple logistic (discrete variables) regression.

* Confirmed by inspection of medical records or interviews with pediatricians by experienced clinical dysmorphologists.
† Excluding stillbirths and fetal deaths.

AED = antiepileptic drug.

EURAP, International Lamotrigine Study) obtain their information from health care professionals. It is likely that the women who participate in the AED Pregnancy Registry do not represent the entire population of pregnant women exposed to AEDs living in North America. The extent of such participation bias has not been determined. Finally, this and other pregnancy individual registries are not designed to study the long-term effects of prenatal exposure to VPA, such as developmental delay and specifically autism, which has been described as related outcome in two case reports[40] and one case series.[41] A prospective study would require hundreds of VPA-exposed children and a study design for long-term follow-up, including testing cognitive function, to address these associations with adequate statistical power.

The risk for women taking VPA of having a baby with an NTD is about 2 to 5%.[17,18,42] Thus, in our sample of 149 VPA-exposed women, two to eight infants with NTD would be expected and three were

observed. The mothers of all 16 cases with congenital anomalies in the VPA-exposed group took either multivitamins containing folic acid or folic acid supplements during the periconceptional period. The three cases with spina bifida were among the 106 VPA-exposed women who took the daily recommended amount of folic acid (prevalence: 2.8%; 95% CI: 0.6 to 8.0%). These findings are in agreement with one case report[43] of the occurrence of spina bifida in spite of periconceptional supplementation with folic acid. The dose of folic acid supplementation in each mother of a malformed infant listed in table 1 was, on average, 1.36 mg, with a range of 0.4 to 5 mg. This finding in this case series should not be considered a definitive assessment of whether or not periconceptional supplementation with folic acid prevents the occurrence of spina bifida when the mother is taking VPA as monotherapy. However, recent data[44] have shown that folic acid supplementation in women taking carbamazepine can reduce the risk of occurrence of spina bifida.

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